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Original Article

Serum osteoinductive factor (OIF) as a predictive biomarker for type II diabetic patients with osteopenia or osteoporosis

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Abstract: Objective: Increased risk of osteoporosis in patients with diabetes is confirmed. However, earlier biomarker as a diagnostic tool for diabetic osteopenia and osteoporosis is absent on clinical diagnosis. Osteoinductive factor (OIF) is known to be an essential component of the bone matrix. We aimed to investigate the relationship between OIF and 2 diabetes mellitus in combination with osteopenia or osteoporosis, and discussed the availability of the serological markers for diabetic osteopenia or osteoporosis screening. Methods: One hundred and twenty subjects were divided into four groups, including healthy controls group (Control, n = 30), patients with type 2 diabetes mellitus group (DM, n = 30), type 2 diabetes mellitus with osteopenia (DOA, n = 42) and type 2 diabetes mellitus with osteoporosis (DOP, n = 18). Serum OIF levels were examined by ELISA, and other clinical biochemical parameters were tested based on standard methods. Results: OIF concentration in diabetic osteopenia and osteoporotic patients was significantly increased as compared to diabetic patients and healthy controls. Serum OIF was strongly correlated for urine calcium in diabetic osteopenia ($r = 0.517$, $P = 0.0005$) and osteoporosis patients ($r = 0.779$, $P < 0.0001$). Moreover, we observed a significant and negative correlation between serum OIF and T-score in osteopenia and osteoporosis patients. Furthermore, the ROC curves illustrated strong separation between the control group and diabetic osteopenia group, with an AUC of 0.793 (95% CI: 0.668-0.919; $P < 0.001$) for OIF. Moreover, the ROC curves indicated that there was strong separation between the control group and diabetic osteoporosis group, with an AUC of 0.878 (95% CI: 0.776-0.977; $P < 0.001$) for OIF. Conclusions: OIF provided the highly diagnostic power for the detection of diabetic osteopenia or osteoporosis, suggesting that serum OIF could serve as a promising marker for diabetic osteopenia or osteoporosis diagnosis.

Keywords: Type 2 diabetes mellitus, osteopenia, osteoporosis, osteoinductive factor, biomarker

Introduction

Diabetes mellitus (DM) is an important endocrine metabolic dysfunctional disease. There is growing evidence corroborating that diabetes mellitus influences the skeletal metabolism [1]. Osteoporosis and falls are related to fractures, which can lead to increased morbidity and mortality, as well as decreased functional ability. Therefore, the prevention of bone fractures is an important goal in a society with increasing longevity [2]. It is recognized that patients with type 2 diabetes mellitus (DM2) are increasing in the worldwide, and a meta-analysis has shown that diabetic patients have a higher hip fracture risk than normal healthy controls [3, 4]. Recent clinical surveys demonstrate that among postmenopausal women with DM2, the average size and the number of holes within the trabecular bone network at the distal radius is greater than those of controls [5, 6]. Moreover, a summary estimates for hip fracture has found that the risk ratio is 6.9 in DM1 and 1.4 in DM2 as compared to subjects without diabetes, respectively [3]. However, the fracture risk is higher despite a higher bone mineral density in DM2 [7]. These results indicate that the characteristic of cause and pathogenesis of diabetic osteoporosis can be very complicated. Thus, the significance of exploration of new biomarkers with high sensitivity and specificity in early detection of diabetic osteoporosis should be emphasized.

Osteoinductive factor (OIF), it is also named osteoglycin, belongs to the small leucine-rich

Table 1. Physiological and biochemical parameters of patients and control group

	Control (n = 30)	DM (n = 30)	DOA (n = 42)	DOP (n = 18)
Age (Years)	50.1 ± 2.1	49.8 ± 2.0	50.6 ± 2.1	50.8 ± 2.0
Sex ratio (M/F)	1.5	2.3	2	1.6
BMI (kg/m^2)	22.9 ± 2.7	23.6 ± 3.3	24.2 ± 3.5	23.6 ± 2.6
SBP (mmHg)	120.5 ± 3.8	123.4 ± 4.2	139.6 ± 5.4$^{*,\#}$	142.1 ± 5.2$^{*,\#}$
DBP (mmHg)	83.2 ± 2.7	85.4 ± 3.3	91.5 ± 3.7*	93.5 ± 3.5$^{*,\#}$
FGB (mmol/L)	5.03 ± 0.11	9.57 ± 0.54*	10.45 ± 0.78*	10.69 ± 0.82*
HbA1c (%)	5.25 ± 0.50	7.8 ± 0.72*	8.13 ± 0.79*	8.18 ± 0.80*
BUN (mmol/L)	4.18 ± 0.39	6.14 ± 1.20*	7.57 ± 2.41*	9.68 ± 3.56$^{*,\#,\&}$
Creatinine (mg/dL)	62.3 ± 4.2	65.7 ± 5.97	88. 6 ± 12.6$^{*,\#}$	131.7 ± 18.4$^{*,\#,\&}$
eGFR	112.4 ± 4.7	138.3 ± 5.9*	121.6 ± 7.1$^{*,\#}$	81.5 ± 4.6$^{*,\#,\&}$

M, male; F, female; FBG, fasting blood glucose; DM, type 2 diabetes mellitus; DOA, type 2 diabetic osteopenia; DOP, type 2 diabetic osteoporosis; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; BUN, blood urea nitrogen; eGFR, Estimated glomerular filtration rate. Values are expressed as mean ± SD. $^{*}P < 0.05$, versus control group; $^{\#}P < 0.05$, versus DM group, $^{\&}P < 0.05$, versus DOA group.

repeat proteoglycan (SLRP) family and is a secretory protein [8]. OIF is initially isolated from bovine bone and found to induce ectopic bone formation [9, 10]. Previous studies have been reported that OIF exerts its function through associating with transforming growth factor β (TGF-β)-like bone morphogenetic proteins [11]. OIF can stimulate proliferation and alkaline phosphate (ALP) activity of osteoblastic cells and bone marrow stromal cells, in contrast, OIF appears to inhibit formation of human osteoclast-like cells and cause a decrease in tartrate-resistant acid phosphatase (TRAP) activity as well as a reduction in oxygen-derived free radical generation in osteoclasts [12, 13]. OIF may be an endogenous inhibitor of continued osteoclastic activity during the resorption of bone. This cessation of osteoclast activity may be an essential preliminary step to the new bone formation that occurs at resorption sites during bone remodeling [13]. Intriguingly, the results of our previous study indicated that serum OIF levels were significantly increased in diabetic nephropathy (DN) subjects compared with healthy and DM2 subjects, and OIF may be an indicator of the earlier-stage DN in subjects with DM2 [14]. However, for all we know, no literature has been reported regarding the serum OIF levels for early screening of diabetic osteopenia or osteoporosis from DM2.

Therefore, the aim of the present work was to investigate the involvement of the serum OIF in DM2 patients with osteopenia or osteoporosis. We were examined the levels of OIF in serum, and its potential use as a biomarker for diabetic osteoporosis detection were evaluated.

Materials and methods

Patients and specimens

This study included a total of 120 subjects contained those with type 2 diabetic mellitus (T2DM, n = 90), and their respective age and sex-matched controls (n = 30), and they were recruited from the Henan Provincial People's Hospital of Zhengzhou University. T2DM was diagnosed according to American Diabetic Association criteria. All healthy subjects were selected based on the results of a physician's questionnaire and laboratory tests. The study was approved by the local ethical committee of Henan Provincial People's Hospital of Zhengzhou University and informed consent was obtained from every subject. Serum and early morning urine samples were collected, centrifuged, aliquot and stored at -80°C until various routine laboratory test and quantification by ELISA.

Physiological and biochemical parameters

Clinical examination and assessment of body mass index (BMI) were performed. Blood pressure was measured 3 times, and the average value was considered for data analysis. Glycosylated haemoglobin (HbA1c) was quantitatively detected by ion exchange chromatography (Stanbio Laboratory). Fasting plasma glucose (FBG) was estimated using glucose oxidase enzymatic assay (Bio Merieux). Calcium (Ca), phosphorus (P), magnesium (Mg) and creatinine (Cr) concentrations of serum and urine were measured by standard colorimetric methods using a micro-plate reader (Bio-Tek, U.S.A.). The level of urine Ca was corrected by the concentration of urine Cr.

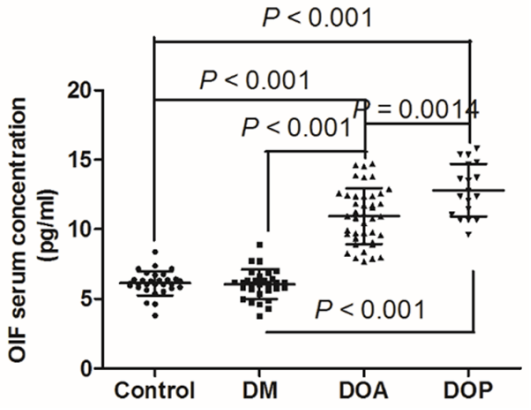

Figure 1. Serum concentration of osteoinductive factor (OIF) among healthy controls group (Control), patients with type 2 diabetes mellitus group (DM), type 2 diabetes mellitus with osteopenia (DOA) and type 2 diabetes mellitus with osteoporosis (DOP) was measured by ELISA analysis.

ELISA

The concentration of OIF in serum was measured with an ELISA kit (Zymed Laboratories Inc, USA) using ab126749 (Abcam, China) as the OIF-specific antibody. The standard curve was created using the suppliers' OIF. And the assay was performed according to the manufacturer's specifications.

Dual-energy x-ray absorptiometry (DEXA)

Bone mineral density (BMD) was measured at the lumbar (L2-L4, LS) and at the femoral neck by dual-energy x-ray absorptiometry (DXA) using a Hologic 4500 bone densitometer. Reference data provided by Hologic for Caucasian populations were used to compare the patients' measurements with age- and sex-matched normal BMD data and to calculate T-scores, according to the WHO criteria [osteoporosis (T-score < -2.5 SD), osteopenia (T-score from-1 to-2.5 SD) and normal (T-score > -1 SD)] [15].

Statistical analysis

Data were described as mean ± standard deviation. Comparison between the two groups was performed using the Student's unpaired t-test. A receiver operating characteristics (ROC) analysis was performed to calculate the area under the curve (AUC) to find the best cutoff values providing the highest diagnostic specificity followed by the best sensitivity. All analyses were performed with Statistical Package for Social Sciences version 13.0 (SPSS, Chicago, IL). In all

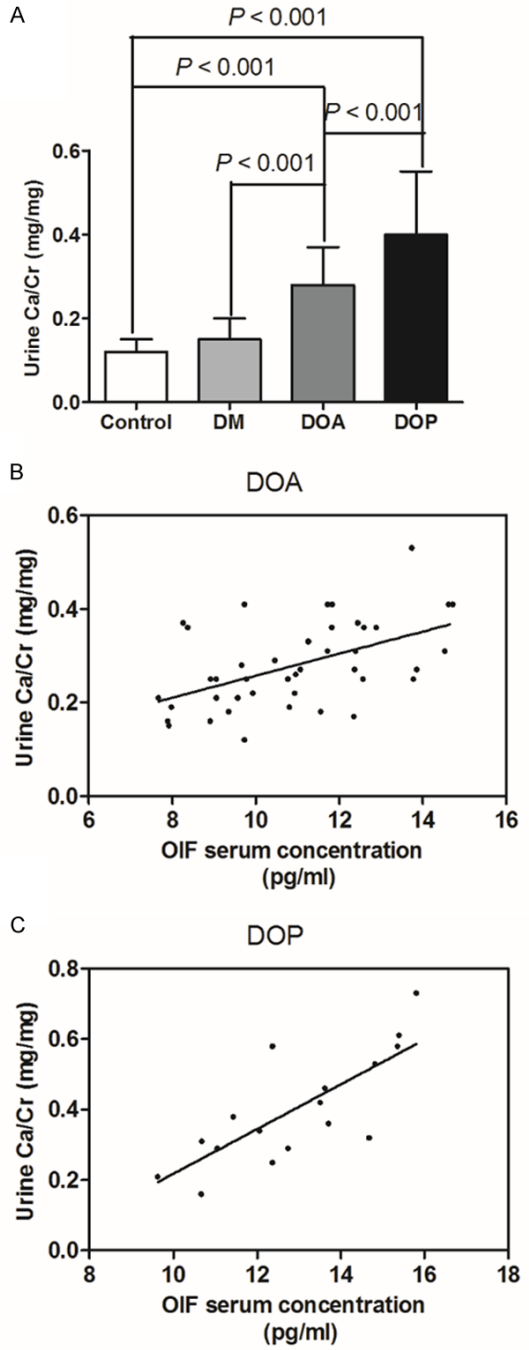

Figure 2. Urine calcium levels were detected by colorimetric method among healthy controls group (Control), patients with type 2 diabetes mellitus group (DM), type 2 diabetes mellitus with osteopenia (DOA) and type 2 diabetes mellitus with osteoporosis (DOP) (A). Linear correlation plot of serum OIF and urine calcium in diabetic osteopenia (DOA) patients (B). Linear correlation plot of serum OIF and urine calcium in diabetic osteoporosis (DOP) patients (C).

Table 2. Mineral metabolism in serum of patients and control group

	Control (n = 30)	DM (n = 30)	DOA (n = 42)	DOP (n = 18)
Ca (mg/dl)	10.27 ± 0.43	9.36 ± 0.57	8.72 ± 0.62*	8.24 ± 0.60*,#
P (mg/dl)	5.81 ± 0.46	5.42 ± 1.03	5.63 ± 0.86	5.45 ± 1.07
Mg (mg/dl)	2.46 ± 0.31	2.37 ± 0.47	2.67 ± 0.52	2.48 ± 0.57
Intact PTH (pg/ml)	62 ± 17	103 ± 25*	145 ± 31*,#	152 ± 42*,#

Ca, calcium; P, phosphate; Mg, magnesium; PTH, parathyroid hormone. Values are expressed as mean ± SD. *$P < 0.05$, versus control group; #$P < 0.05$, versus DM group.

statistical tests, differences with *P*-values < 0.05 were considered as significant.

Results

Basic parameters and biomarker in serum

Clinical and biochemical profiles of the subjects enrolled in the study are shown in **Table 1**. There was no significant difference in age, sex ratio and BMI among the four experimental groups. Compared to the healthy control and DM group, the systolic pressure and diastolic blood pressure were significantly increased in diabetic osteopenia and diabetic osteoporosis group. Moreover, the levels of FGB and HbA1c were markedly upregulated in DM, DOA and DOP group as compared to those of control group. However, FGB and HbA1c had no obvious difference among the three diabetic groups. Notably, BUN and creatinine in DOP group were significantly higher than another three groups, but with the eGFR the opposite was the case.

OIF was upregulated and associated with disequilibrium of calcium homeostasis in DOA and DOP patients

OIF plays a key role in the interaction between osteoblasts and osteoclasts, which may contribute to the bone remodeling [12]. To further validated the interaction between the serum OIF and bone deteriorations in diabetic patients, ELISA was performed to identify the serum concentration of OIF among all the experimental groups. The results showed that OIF concentration in diabetic osteopenia and osteoporotic patients was significantly increased as compared to diabetic patients and healthy controls (**Figure 1**). Additionally, the results showed that the serum OIF and urine calcium levels in DOP group were significantly higher than that of the DOA group (**Figures 1**, **2A**). Moreover, mineral metabolism in serum of patients and control group was investigated. Serum phosphate and magnesium had no obvious difference among the four experimental groups. Notably, serum calcium in DOA and DOP patients was 8.72 ± 0.62 mg/dl and 8.24 ± 0.60 mg/dl respectively, which was significantly lower than in non-diabetic controls (**Table 2**). In contrast, the urine calcium was increased in DOA and DOP patients as compared to that of healthy control (**Figure 2A**). Serum intact PTH, a biochemical marker for regulating calcium homeostasis, did not differ significantly between the DOA group and DOP group. However, serum intact PTH in DOA and DOP patients was 145 ± 31 pg/ml and 152 ± 42 pg/ml respectively, which was significantly higher than in non-diabetic controls (**Table 2**). To test whether there was a relationship between serum OIF and urine calcium levels, which was measured in diabetic osteopenia and osteoporosis patients. As shown in **Figure 2B**, measurements obtained from serum OIF was strongly correlated for urine calcium in diabetic osteopenia patients (**Table 3** and **Figure 2B**; r = 0.517, $P = 0.0005$). Intriguingly, the higher correlation was detected in DOP patients between urine calcium and serum OIF (**Table 3** and **Figure 2C**; r = 0.779, $P < 0.0001$). As shown in **Table 4**, both lumbar and femoral neck BMD were significantly decreased in diabetic osteopenia and osteoporosis patients as compared to healthy subjects and diabetic patients, and T-score of lumbar and femoral neck obtained from diabetic osteopenia and osteoporosis patients was obvious lower than that of the healthy subjects and diabetic patients. Compared to diabetic osteopenia patients, the BMD and T-score of lumbar and femoral neck were lower in diabetic osteoporosis patients. We observed a significant and negative correlation between serum OIF and T-score. The correlation was more pronounced in lumbar and femoral neck with diabetic osteoporosis patients ($r = -0.837$, $P < 0.0001$ and $r = -0.643$, $P = 0.0004$) than lumbar and femoral neck with diabetic osteopenia patients ($r = -0.529$, $P = 0.0004$ and $r = -0.500$, $P = 0.0008$; **Table 3** and **Figure 3A-D**).

Table 3. Correlation of serum OIF with urine Ca and T-score in DOA and DOP patients

		DOA (n = 42)	DOP (n = 18)
Serum OIF vs. Urine Ca	Spearman r	0.517***	0.779***
	95% confidence interval	0.252 to 0.709	0.490 to 0.913
	P value (two-tailed)	0.0005	< 0.0001
Serum OIF vs. T-score (lumbar)	Spearman r	-0.529***	-0.837***
	95% confidence interval	-0.717 to -0.268	-0.937 to -0.607
	P value (two-tailed)	0.0003	< 0.0001
Serum OIF vs. T-score (femoral neck)	Spearman r	-0.500***	-0.643***
	95% confidence interval	-0.698 to -0.231	-0.854 to -0.252
	P value (two-tailed)	0.0008	0.0004

***$P < 0.001$.

Table 4. Bone mineral density of patients and control group

	Control (n = 30)	DM (n = 30)	DOA (n = 42)	DOP (n = 18)
Lumbar BMD (g/cm^2)	1.13 ± 0.15	1.15 ± 0.28	0.91 ± 0.21$^{*,\#}$	0.78 ± 0.18$^{*,\#,\&}$
Femoral neck BMD (g/cm^2)	0.97 ± 0.10	0.95 ± 0.15	0.81 ± 0.16$^{*,\#}$	0.77 ± 0.14$^{*,\#}$
T-score (SD) lumbar BMD	-0.35 ± 0.51	-0.38 ± 0.62	-1.60 ± 0.31$^{*,\#}$	-2.91 ± 0.32$^{*,\#,\&}$
T-score (SD) femoral neck BMD	-0.41 ± 0.49	-0.53 ± 0.41	-1.34 ± 0.20$^{*,\#}$	-2.20 ± 0.36$^{*,\#,\&}$

DM, type 2 diabetes mellitus; DOA, type 2 diabetic osteopenia; DOP, type 2 diabetic osteoporosis; BMD, bone mineral density, SD, standard deviation. Values are expressed as mean ± SD. $^{*}P < 0.05$, versus control group; $^{\#}P < 0.05$, versus DM group, $^{\&}P < 0.05$, versus DOA group.

Receiver operating characteristic (ROC) curve analysis of OIF in serum from DOA and DOP patients

To investigate the characteristics of OIF as potential markers of diabetic osteopenia or osteoporosis. ROC curve and the area under the ROC curves (AUC) were performed on data from all subjects. The ROC curves illustrated strong separation between the control group and diabetic osteopenia group, with an AUC of 0.793 (95% CI: 0.668-0.919; $P < 0.001$) for OIF (**Figure 4A**). Moreover, the ROC curves indicated that there was strong separation between the control group and diabetic osteoporosis group, with an AUC of 0.878 (95% CI: 0.776-0.977; $P < 0.001$) for OIF (**Figure 4B**). Moreover, the sensitivity, specificity, accuracy, Youden Index, Cut off, PPV and NPV of OIF for distinguishing DOA and DOP were summarized in **Table 5**.

Discussion

Diabetes mellitus (DM) results in hyperglycemia because of an insulin insufficiency or insulin resistance, which leads to many complications, such as both microvascular and macrovascular pathological changes [16], retinopathy [17], diabetic nephropathy [18] and diabetic osteoporosis [19]. Emerging data strongly implicate OIF in the basal regulation of osteoblasts and osteoclasts function, which is central to calcium homeostasis and bone remodeling [12, 13]. Mounting evidences have showed that OIF play a central role in the regulation of cell development, differentiation and proliferation [12, 13]. So identification of bone metabolism associated biomarker is critical and may be important for novel therapeutic targets and improve the clinical strategies of osteoporosis. In our previous study, the results indicate that serum OIF levels are significantly increased in diabetic nephropathy (DN) subjects compared with healthy and DM2 subjects, and OIF is a sensitive marker for early microalbuminuria. These data indicated that OIF may be a potential biomarker for diagnosing and evaluating the onset and development of DN among DM subjects [14].

In this study, we demonstrated that the increase in OIF levels were confirmed by ELISA assays in

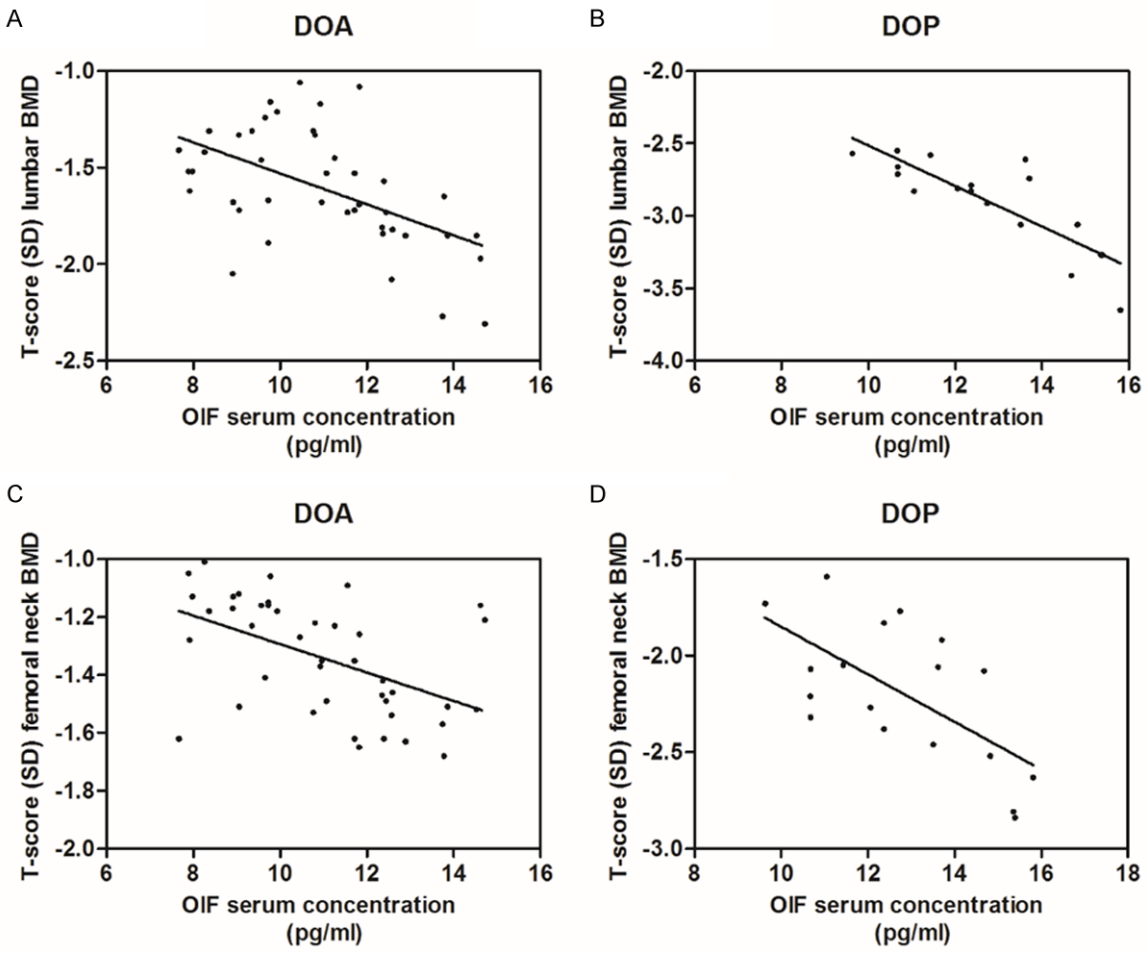

Figure 3. Linear correlation plot of serum OIF and T-score (SD) lumbar BMD in diabetic osteopenia (DOA) patients (A). Linear correlation plot of serum OIF and T-score (SD) lumbar BMD in diabetic osteoporosis (DOP) patients (B). Linear correlation plot of serum OIF and T-score (SD) femoral neck BMD in diabetic osteopenia (DOA) patients (C). Linear correlation plot of serum OIF and T-score (SD) femoral neck BMD in diabetic osteoporosis (DOP) patients (D).

diabetic osteopenia or osteoporosis patients as compared to healthy subjects and diabetic patients. Next, the higher correlation was detected in DOA or DOP patients between urine calcium and serum OIF. The serum calcium and urine calcium had no obvious difference in DM group as compared to control group, moreover, there was no significant correlation between serum OIF and urine calcium in DM group (date no shown). These results suggested that serum OIF levels had obvious difference in the morbidity process of diabetic complications, especially the progression of diabetic osteopenia or osteoporosis. The comparison of BMD distribution with a population-based control group suggests a lower risk of osteoporosis in type 2 diabetes, however, the prevalence of fragility fractures was not different between patients with type 1 and type 2 diabetes [19]. Interestingly, lumbar BMD and femoral neck BMD may be increased in patients with type 2 diabetes in comparison with a population-based control group confirms similar findings from epidemiological studies [19, 20]. There is growing evidence for an increased risk of fractures in patients with diabetes mellitus despite normal or even high BMD values [3, 21]. In our work, both lumbar and femoral neck BMD were significantly decreased in diabetic osteopenia and osteoporosis patients as compared to healthy subjects and diabetic patients, and T-score of lumbar and femoral neck obtained from diabetic osteopenia and osteoporosis patients was obvious lower than that of the healthy subjects and diabetic patients. The assessment of serum OIF and diabetic osteopenia or osteoporosis specific parameters showed highly negative relationships. Underline the clinical impor-

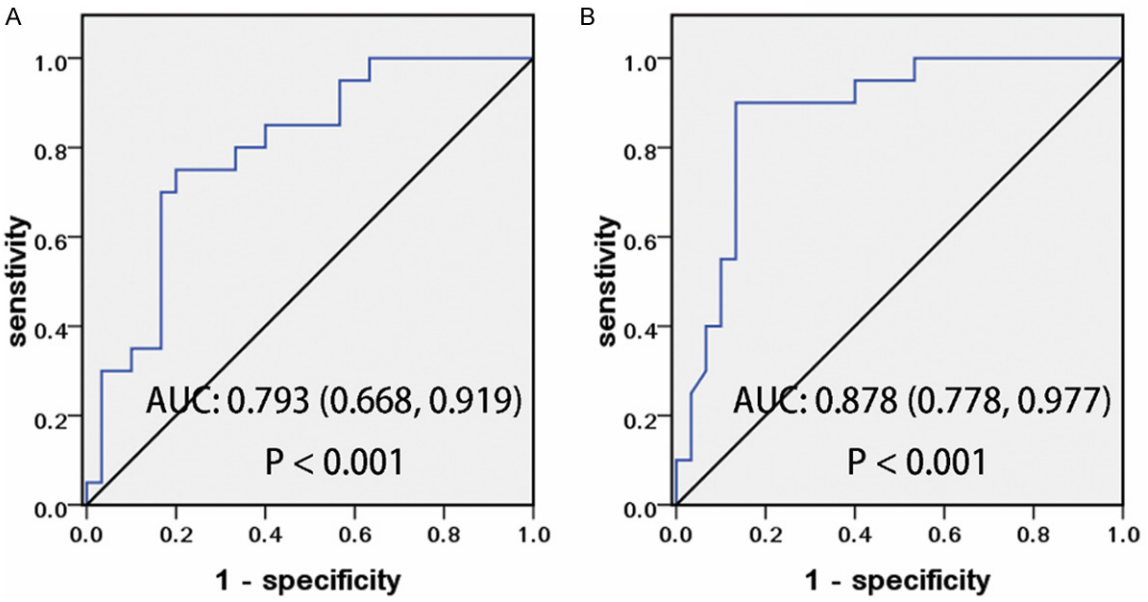

Figure 4. The ROC curve of OIF levels for distinguishing diabetic osteopenia or osteoporosis patients from type 2 diabetes mellitus patients. The area under the ROC curve (AUC) was calculated for the diagnosis of diabetic osteopenia patients (A) and diabetic osteoporosis patients (B).

Table 5. ROC related parameters

	Sensitivity	Specificity	Accuracy	Youden Index	Cut off	PPV	NPV
DOA	80.9%	80.0%	83.3%	60.9%	10.5	85.0%	75.0%
DOP	88.9%	90.0%	89.6%	78.9%	12.4	84.2%	93.1%

DOA, type 2 diabetes mellitus with osteopenia; DOP, type 2 diabetes mellitus with osteoporosis; PPV, positive predictive value; NPV, negative predictive value.

tance of changes in serum OIF as a biomarker associated with type 2 diabetes mellitus in combination with bone metabolism disturbance. In recent decades, there are less pronounced about serum OIF in diabetic complications, which is probably underestimated and deserves more consideration during diabetic osteopenia and osteoporosis screening.

OIF has a high sensitive and specificity for the prediction of microalbuminuria (86.7% and 95%, respectively) and macroalbuminuria (90% and 95%, respectively) in our previous study [14]. In the present study, the ROC curves illustrated strong separation between the control group and diabetic osteopenia group, with an AUC of 0.793 (95% CI: 0.668-0.919; $P < 0.001$) for OIF. Moreover, the ROC curves indicated that there was strong separation between the control group and diabetic osteoporosis group, with an AUC of 0.878 (95% CI: 0.776-0.977; $P < 0.001$) for OIF. Therefore, OIF provided the highly diagnostic power for the detection of diabetic osteopenia or osteoporosis, suggesting that serum OIF could serve as a promising marker for diabetic osteopenia or osteoporosis diagnosis.

In conclusion, the clinical evidences in this study revealed that serum concentrations of OIF were increased in subjects with diabetic osteopenia and osteoporosis. OIF was a sensitive marker for bone deteriorations. These data indicated that OIF might be a potential biomarker for diagnosing and evaluating the onset and development of osteopenia or osteoporosis among DM subjects.

Disclosure of conflict of interest

None.

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